CHAPTER 6

Design, Development & Optimization of Colon Targeted Multi-Particulate System
6.1) INTRODUCTION

Oral controlled release drug delivery systems can be classified into two broad groups: single unit systems, such as tablets or capsules, and multiple unit systems such as granules, pellets or minitablets (MT’s). In the earlier chapters (Chapter 3 & 4), double coated systems were developed, where compression coating followed by enteric coating. The basic drawbacks of these double coated systems are: 1) Time consuming process, 2) Tedious method of preparation, 3) Process expertise is needed for compression coating, and 4) Costly process.

Apart from being double coated systems they were single unit systems. The single unit systems may add to the problem of dose dumping in non-target areas. Multiple-unit systems can be classified into granules, pellets and MT’s. MT’s are good substitutes for granules and pellets because they can be manufactured relatively easily, and are amenable to coating in order to target drug release. The production of MT’s using a tableting technique is an attractive alternative to the production of pellets, as the presence of solvents (e.g., water) is avoided and high production yields like the ones observed in extrusion and spheronization are obtained. Furthermore, due to the ease and reproducibility in manufacturing process, defined size and strengths can easily be produced, with small variability within and between batches.

MT have basically been used for formulating controlled drug delivery system using HPMC, ethylcellulose, polyvinylacetate/polyvinylpyrrolidone, calcium alginate, calcium alginate/guar gum, polyvinylacetate, cellulose acetate propionate, xanthan gum, karaya gum and starch/microcrystalline wax. Coated oral sustained-release forms of drugs are widely used to improve drug tolerance or to yield a dosing regimen that is easier to manage for patients. However, little published information is available on pulsatile release systems using coated MT. Pulsatile drug delivery system has the advantage of avoiding drug tolerance or matching the chronotherapeutic needs.

The oral pulsatile release systems have mainly been used for the treatment of disease symptoms such as hypertension, ischemic heart disease, asthma and rheumatoid arthritis, which exhibit circadian rhythms. The required amount of drug releases from the drug delivery system at the required time of night or early morning.

In this chapter an effort was made to formulate coated MT’s as multiple-unit colon targeted pulsatile drug delivery systems. The move to explore the feasibility of multiple-unit system for colon targeting was based on the fact that they display...
uniform gastric emptying time. MT’s are generally of the size of 2 – 3 mm.\textsuperscript{26,27} In the present work due to dose constraints MT’s were used, which have lately been used by other researchers\textsuperscript{28-30} also. The concept of multiple-unit systems is characterized by the fact that the dose is administered as a number of subunits, each one containing the drug. The dose is then the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits.\textsuperscript{31-33}

The single unit systems prepared for colon targeted drug delivery become very bulky, due to unavoidable double coating. The weight of single unit double coated systems reaches as high as 1 g. Moreover, due to bigger size the tablets may not follow normal gastric emptying patterns, which may lead to dose dumping in non-target areas. In order to avoid the possible complexities, use of multiunit systems such as CTDDS was explored.

6.2) MATERIALS AND METHODS

MATERIALS
List of materials and instruments are mentioned in Appendix I

METHODS
Method of identification of MTZ, development of calibration curve of MTZ and drug-excipient compatibility study are discussed in chapter 3.

6.2.1) Preparation of core mini-tablets MT’s
Weighed quantity of MTZ, lactose (diluent) and swelling agent (5% Sodium carboxymethylstarch or Cross-linked polyvinyl- pyrrolidone) were passed through 30# sieve. All the ingredients were mixed for 15 min in bin blender. Binding solution was added to the above blend to prepare a dough mass. The dough mass was forced though 16# sieve and the granules so obtained were dried at 40 ± 5 °C in a tray dryer. The dried granules were passed through 24# sieve. Talc and magnesium stearate were sifted through 40# sieve. The dried granules were lubricated with talc and magnesium stearate for 5 min in a bin blender. The lubricated granules were compressed tablet.

6.2.2) Evaluation for dried granules of MTZ
Dried granules were checked for its flowability and compressibility as per the methods described in chapter 3.
6.2.4) Evaluation of core MT’s
Core MT’s were evaluated for hardness, thickness and weight variation as per the method described in chapter 3.

6.2.5) In-vitro evaluation of MT’s
a) Uncoated MT’s
Drug release studies for uncoated MT’s of MTZ were carried out using a XXIII dissolution rate test apparatus (Type 2: paddle apparatus, 100 rpm, 37± 0.5 °C) in 900 ml pH 6.8 phosphate buffer solution (SCF) and tested for drug release upto 100% drug release. At the end of the time period, 5 ml of the samples were withdrawn and filtered with whatman filter paper (0.45 microns pore size) and analyzed for MTZ content as described previously. Withdrawn volume of dissolution medium was replaced with fresh dissolution medium. The drug release at different time intervals was analyzed by UV double beam spectrophotometer at 320.4 nm in SCF. Each test was performed in triplicate.

b) Coated MT’s
In-vitro drug release studies for coated MT’s were carried out using USP XXIII dissolution test apparatus Type II, paddle apparatus (100 rpm/min, 37+ 0.5 °C). MT filled in capsule were evaluated for in-vitro drug release by exposing them to 900 ml 0.1 N HCl (SGF) for 2 h which was later replaced by 900 ml pH 7.4 phosphate buffer solution (SIF), wherein it was kept for 3 h. Later it was replaced with 900 ml SCF (pH 6.8 phosphate buffer solution) for the entire study. The drug release at different time intervals was analyzed by UV double beam spectrophotometer at 276.5 nm in SGF, 319.4 nm in SIF and 320.4 nm in SCF. Each test was performed in triplicate.

6.2.6) In-vivo animal study
The protocol for the present study was approved by the Institutional animal ethics committee.

Grouping of animals
Animals were divided in 2 groups of 3 animals each.
Group 1: Uncoated tablets
Group 2: Optimized final formulation
6.2.7) Assay method
MTZ concentrations in plasma samples were analysed by a HPLC method.

a) Chromatographic Conditions
A reversed phase HPLC method was developed to quantitate plasma levels of MTZ.

b) Calibration curve
A stock solution of MTZ was prepared by dissolving 100 mg in 100 ml of methanol. Calibration curves, which were based on peak-area to the concentration of the drug, were prepared by spiking drug-free plasma with a standard MTZ (1 mg/ml) to give a concentration range. Plasma drug concentrations in samples were calculated by determination of the peak area of MTZ and comparing the area with those of the standard curve which was obtained after analysis of calibration samples.

c) Within-day Variability
The within-day variability of the assay was determined by repeated analysis (6 times) of samples for quality control on same day.

d) Between-day Variability
The between-day variability of the assay was determined by repeated analysis of samples for quality control at 6 consecutive days.

6.2.8) Design of Experiment (DOE)
On the basis of preliminary trials, a 2-factor 3-level factorial design was selected as an optimization process for preparation Colon targeted MT.

6.2.9) Stability Study
Optimized SR formulations of MTZ were packed in 75 cc HDPE bottles and stability study was carried out as per the procedure mentioned in chapter 3.
6.3) RESULTS & DISCUSSION

6.3.1) Drug-excipient compatibility study
The prototype blend observed physically, after the stability study did not show liquefaction, caking, odor, gas formation or discoloration.
From the FTIR and DSC results it can be concluded that API is compatible with other excipients of the formulation and thus can be used for further studies.

6.3.2) Granulometric analysis of MTZ granules
Overall the granules showed good compressibility and flow. The ratio of coarse is to fine granules was also found good (>50% granules were coarse) for both. Granules were suitable for preparation of MT’s.

6.3.3) Physical and chemical evaluation of optimized core MT’s
Optimized core MT’s (batch M1) were subjected to physical and chemical evaluation along with in-vitro drug release study.

6.3.5) DOE study
In the preliminary study coating level was kept constant at 7%. To simultaneously check the effect of amount of A in the mixed coat of A:B and % coating level on drug release it was decided to use statistical approach for method optimization i.e. DOE study.

6.3.7 Stability Study
Physical appearance of all the stability batches of Q10 was similar to the fresh batches. $f_2$ value between initial and 3 month stability sample and 6 month stability sample was similar to original. The $f_2$ value above 50 is indicative of statistical similarity of the two release profile. Thus, Batch Q10 was considered as the best batch for delivering MTZ to the colon.

6.3.8) Assay of MTZ
Optimized batch Q10 was selected for in-vivo study. MTZ concentrations in plasma samples were analysed by a HPLC method. The same procedure was used for preparation of plasma samples, as for calibration curve construction and for quality control (QC) samples.
A rapid, sensitive HPLC method was described for the determination of MTZ in human plasma. Protein precipitation with acetonitrile followed by a step of freezing allowed an efficient separation of aqueous and organic phases, and therefore
improved the limit of quantitation. Polar interferences are therefore decreased which affords a gain in signal to noise ratio and column life is likewise greatly extended. This analytical procedure can be readily applied to routine analysis of plasma samples for bioavailability and pharmacokinetic study.

6.3.9) In-vivo study

The single dose pharmacokinetic study was carried out for uncoated tablets and colonic tablets (batch Q10).

From in-vitro study it was clear that, for colonic tablet (batch Q10), time required for 100% drug release is 7.4 h, which is close to in-vivo time point of 7 h for colonic tablet. Thus, batch Q10 can be considered as best batch for targeting MTZ to colon.

6.4) CONCLUSION

The colonic tablets were designed to prevent drug release in stomach and release drug rapidly after predetermined lag time in the intestinal tract when the system reaches the colon. The system consists of a core containing a drug (MTZ), coated with A and B® S. Prior to drug release, B® S dissolved in an environment of pH above 7 and causes pores in the coating film. Water penetrates through pores of the film into the core and diffuses the drug out. The lag time could be controlled by the thickness of the coating film. The in-vivo study also indicates that the designed system can release the drug in the gastrointestinal tract in a manner similar to that in-vitro. The designed system resembles to the pulsatile release tablets, and thus may be considered to be suitable for the use in drugs which are expected to exhibit therapeutic effects several hours after taking medicine, e.g., from midnight to daybreak.

6.5) REFERENCES


